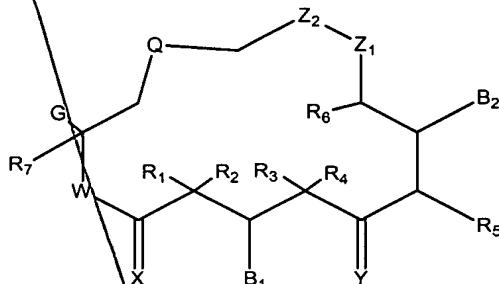


E 2
TOPPO

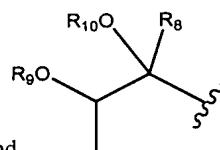
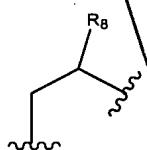
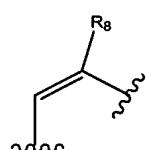
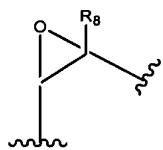
1. (Fourth amendment) A compound of the formula:



V

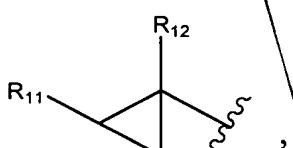
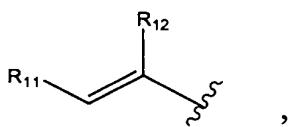
wherein:

Q is selected from the group consisting of:

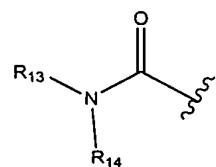


and

XOPP1
G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



and



W is O or NR₁₅;

X is O or H, H;

Y is selected from the group consisting of O; H, OR₁₆; OR₁₇, OR₁₇; NOR₁₈; H, NOR₁₉; H, NR₂₀R₂₁; H, H; and CHR₂₂; wherein OR₁₇, OR₁₇ can be a cyclic ketal;

Z₁ and Z₂ are independently CH₂;

B₁ and B₂ are independently selected from the group consisting of OR₂₄, OCOR₂₅, and O-C(=O)-NR₂₆R₂₇, and when B₁ is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

E1
contd

R₁, R₂, R₃, R₄, R₅, R₇, R₁₃, R₁₄, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₆ and R₂₇ are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R₁ and R₂ are alkyl can be joined to form a cycloalkyl, and when R₃ and R₄ are alkyl can be joined to form a cycloalkyl;

R₆ is methyl;

E2

R₉, R₁₀, R₁₆, R₁₇, R₂₄, R₂₅ and R₃₁ are selected from the group consisting of H, alkyl, and substituted alkyl;

R₁₁, R₁₂, R₂₈, R₃₀, R₃₂, and R₃₃ are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C₃-C₇ carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R₈ is hydrogen or methyl;

R₁₅, R₂₃ and R₂₉ are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C₃-C₇ carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; R₃₂C=O; R₃₃SO₂; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts thereof, hydrates, solvates or geometric, optical or stereoisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R₁, R₂ and R₇ are H; and

R₃, R₄ and R₆ are methyl; and

R₈ is H or methyl; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above

are excluded.

E3
E2

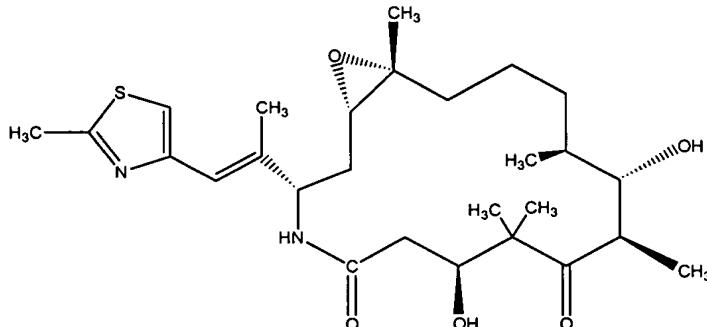
4. (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need

~~of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.~~

~~pf 3
EY~~
~~8.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

~~E5
P4~~
~~7 11.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

~~C6~~
~~T10810~~
~~8 14.~~ A compound having the formula:



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer or stereoisomer thereof.

~~9 15.~~ (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.⁸

E 7 23. (Amended) A method of treating breast cancer, ovarian cancer, colon cancer,

*E 7
G 6* head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.¹³

E 8 19

25. (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.¹⁴

*E 9
G 7* 21

27. (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.¹⁵

*E 10
G 9* 23

29. (Amended) A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.¹⁶

Please add the following new claim:

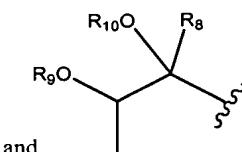
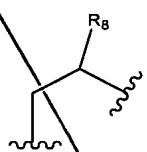
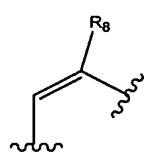
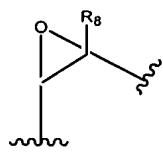
*E 11
G 11* 25.359.

(New) A compound of the formula:

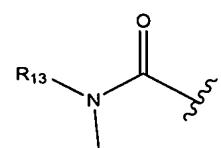
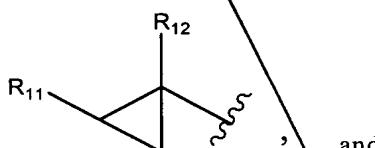
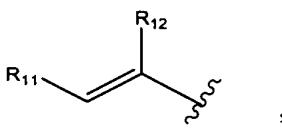
E'
T10030
G'
Cont

wherein:

Q is selected from the group consisting of:



G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



X is O or H, H;

Y is selected from the group consisting of O; H, OR₁₆; OR₁₇, OR₁₇; NOR₁₈; H, NOR₁₉; H, NR₂₀R₂₁; H, H; and CHR₂₂; wherein OR₁₇, OR₁₇ can be a cyclic ketal;

Z₁ and Z₂ are independently CH₂;

B₁ and B₂ are independently selected from the group consisting of OR₂₄, OCOR₂₅, and O-C(=O)-NR₂₆R₂₇, and when B₁ is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

83

e

E 15
~~R₁, R₂, R₃, R₄, R₅, R₇, R₁₃, R₁₄, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₆ and R₂₇ are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R₁ and R₂ are alkyl can be joined to form a cycloalkyl, and when R₃ and R₄ are alkyl can be joined to form a cycloalkyl;~~

~~R₆ is methyl;~~

B 11
cont'd
~~R₉, R₁₀, R₁₆, R₁₇, R₂₄, R₂₅ and R₃₁ are selected from the group consisting of H, alkyl, and substituted alkyl;~~

~~R₁₁, R₁₂, R₂₈, R₃₀, R₃₂, and R₃₃ are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C₃-C₇ carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;~~

~~R₈ is hydrogen or methyl;~~

~~R₁₅, R₂₃ and R₂₉ are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C₃-C₇ carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; R₃₂C=O; R₃₃SO₂; hydroxy; O-alkyl or O-substituted alkyl;~~

~~or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or stereoisomers thereof.~~

54
60. (New) A method of treating breast cancer, ovarian cancer, colon cancer,

B 11
cont'd
~~head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 59.~~⁵³

55
61. (New) The method of claim 60, wherein the cancer is cancer of the breast, ovary, or colon.

E
push
G'12

~~58~~ 62. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 59.⁵³

~~57~~ 63. (New) The method of claim 60, further comprising administering one or more of a additional anti-cancer agent.

~~58~~ 64. (New) The method of claim 63, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G₂-M phase.

~~59~~ 65. (New) The method of claim 64, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclease reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

~~60~~ 66. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 59.⁵³

~~61~~ 67. (New) A pharmaceutical composition comprising the compound of claim 59 and a pharmaceutically acceptable vehicle or diluent.

THE CLAIMED INVENTION

Claims 1-3, 14, 19-22, and 59 of this application are directed to novel molecules wherein the structure of the 16-member cyclic epothilone ring or substituents attached to the 16-member cyclic epothilone ring are modified. Claims 4, 7-8, 11, 15-18, 23-30, 40-42, 51-58, 60-61, and 63-66 are directed to methods of treating cancer in a patient which comprises administering a therapeutically effective amount of a compound of the invention. Claims 31-38 and 62 are directed to methods of treating cancer responsive to microtubule stabilization which comprises administering a therapeutically effective amount of a compound of the invention. Claims 43-50 and 67 are directed to pharmaceutical compositions comprising a compound of the invention.

Applicants note that the Examiner has previously recognized that claim 3 and 14 are free of the art (*See*, Office Action mailed August 29, 2001, Paper No. 15). Indeed, these claims and those dependent from them have not been rejected over any art in the instant Office Action. Claim 3 is not and has not been dependent from claim 1. Thus, there are *no* rejections pending against claim 3. Further, claim 14 has been amended herein to be in independent form. Thus, no rejection stands against claim 14 or claims dependent therefrom. Applicants respectfully request indication that such claims are allowable.

**THE REJECTION UNDER 35 U.S.C. §112,
SECOND PARAGRAPH, SHOULD BE WITHDRAWN**

Claims 1-4, 7-8, and 14-58 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for the reasons set forth on pages 2-3 of the Office Action. The Examiner alleges that the term "substituted" without saying which substituents are intended is indefinite. First, Applicants respectfully traverse this rejection as it is applied to claims 3 and 14 since they do not recite the term "substituted." Thus, the rejection is improper and should be withdrawn.

Applicants respectfully submit that independent claim 1 is not indefinite. "Whether a claim is . . . [indefinite] depends on whether those skilled in the art would understand the scope of the claim when the claim is read in the light of the specification." *North American Vaccine Inc. v. American Cyanamid Co.*, 28 U.S.P.Q.2d 1333, 1339 (Fed. Cir. 1993). Applicants respectfully submit that one of ordinary skill in the art, reading the specification, would readily understand what is meant by the term "substituted." The specification clearly provides a definition for the term "substituted." For example, the term "substituted alkyl" and "substituted aryl" are both defined (*See, e.g.*, Specification, page 4, lines 14-31 and page 5, lines 9-18, respectively). Accordingly, one of ordinary skill in the art, reading the disclosure, would readily understand what scope is meant by the term "substituted."